Published in final edited form as:

Nicotine Tob Res. 2007 December ; 9(12): 1251–1257.

Bupropion efficacy for smoking cessation is influenced by the *DRD2* Taq1A polymorphism: Analysis of pooled data from two clinical trials

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Abstract

We analyzed pooled data from two comparable randomized placebo-controlled clinical trials of bupropion pharmacotherapy for smoking cessation for which data on *DRD2* Taq1A genotype were available. A total of 722 smokers across the two trials were randomized to 10 weeks of sustained-release bupropion hydrochloride or placebo. General estimating equation analysis demonstrated a significant gene $\times$ drug interaction ($B=0.87$, $SE=0.34$, $p=.009$). Smokers with the A2/A2 genotype using bupropion were more than three times as likely, relative to placebo, to be abstinent at end of treatment (35.2% vs. 15.1%; $OR=3.25$, 95% CI 2.00–5.28) and at 6 months of follow-up (26.7% vs. 12.2%; $OR=2.81$, 95% CI 1.66–4.77), which was attenuated by 12 months (16.3% vs. 10.7%; $OR=1.70$, 95% CI 0.95–3.05). We found no significant benefit of bupropion relative to placebo on smoking cessation outcomes at any time point in participants with A1/A1 or A1/A2 genotypes. These data suggest that bupropion may be effective for smoking cessation only in a subgroup of smokers with the *DRD2* Taq1 A2/A2 genotype.

Introduction

Despite major recent public health gains, fewer than 10% of smokers who attempt to quit remain abstinent after years of follow-up (Yudkin et al., 2003), and among persistent smokers, approximately half, or 5 million annually worldwide, die prematurely (Peto et al., 1996). Bupropion, nicotine replacement therapy (NRT), and varenicline are the three first-line, FDA-approved, pharmacological interventions for smoking cessation (Foulds, 2006; Schnoll & Lerman, 2006). Despite the efficacy of these interventions, 70%–80% of patients relapse within

12 months of attempting to quit smoking (Hurt et al., 1997; Jorenby et al., 1999). Therefore, attention has focused increasingly on the prospect of tailored medicine as a means of identifying subgroups of smokers most likely to respond to specific pharmacotherapies, thereby increasing smoking cessation efficacy (Munafò, Shields, Berrettini, Patterson, & Lerman, 2005).

Approximately 50% of the variance in risk for nicotine dependence is attributable to genetic factors (Li, Cheng, Ma, & Swan, 2003). Bupropion has demonstrated dopamine and norepinephrine reuptake and nicotinic acetylcholine receptor antagonist properties (Ascher et al., 1995; Fryer & Lukas, 1999). Given the well-established role of the mesocorticolimbic dopamine reward system in nicotine dependence (Balfour, 2002; Laviolette & van der Kooy, 2004), genes influencing dopamine and bupropion pharmacodynamics and pharmacokinetics are biologically plausible candidates for studying pharmacogenetic response for smoking cessation (Lerman et al., 2006; Lerman & Niaura, 2002).

Of the likely hundreds of candidate genes believed to influence nicotine dependence (Sullivan et al., 2004), the most widely studied genetic variant in pharmacogenetic smoking cessation studies is the *DRD2* Taq1A polymorphism, which was recently found to be present in a newly discovered tyrosine kinase gene (*ANKK1*) located 3' to the *DRD2* gene (Neville, Johnstone, & Walton, 2004). The Taq1A variant may alter the function of the nearby *DRD2* gene and has been reported to affect dopamine receptor D2 availability in postmortem striatal samples (Blum et al., 1990). Evidence from *in vivo* studies indicates an association between the A1 allele and lower mean relative glucose metabolic rate in dopaminergic regions in the human brain (Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997) and low striatal receptor density (Jonsson et al., 1999).

A moderating effect of Taq1A genotype on treatment response has been observed in only one of three published pharmacogenetic studies (David et al., 2007), despite qualitative observations in the other two studies of higher abstinence rates among those using bupropion possessing the *DRD2* Taq1 A2/A2 genotype compared with A1/A1 or A1/A2 genotypes (Lerman et al., 2003; Swan et al., 2003).

To establish whether the *DRD2* Taq1A polymorphism moderates treatment response to bupropion for smoking cessation, we conducted a pooled analysis of data from two comparable pharmacogenetic clinical trials (David et al., in press; Lerman et al., 2003). This analysis provided greater statistical power and allowed a more accurate estimate of the effect of *DRD2* Taq1A genotype on response to bupropion. The other published pharmacogenetic investigation of *DRD2* Taq1A genotype and bupropion efficacy (Swan et al., 2005) was an open-label clinical effectiveness study lacking a placebo-control group. This study could not be in our pooled analyses given our aim of analyzing the relative efficacy (compared with placebo) of bupropion according to the *DRD2* Taq1A genotype.

Method

Procedure

Recruitment methods and study outcomes for both studies have been described elsewhere (David et al., 2007; Lerman et al., 2003). Participants were adult smokers (aged 18–65 years), without medical contra-indications to bupropion. Participants were screened for *DSM-IV* disorders (American Psychiatric Association, 1994) using the Structured Clinical Interview for *DSM* (SCID nonpatient version; First, Spitzer, Gibbon, & Williams, 1989) and excluded for Axis I disorders, with the exception of nicotine dependence.

Both studies were double-blind, randomized, placebo-controlled clinical trials of sustained-release bupropion hydrochloride for smoking cessation, with comparable study protocols,

conducted at two sites: Washington, DC, and Buffalo, NY (Study 1: $n=555$), and Brown University (Study 2: $n=524$). All participants received 10 weeks of either placebo or bupropion (150 mg/day for the first 3 days, then 300 mg/day) plus standardized behavioral group counseling. Target quit dates were set for 1 week following initiation of drug or placebo. Only participants of European ancestry were included in the pooled analysis ($n=722$) to minimize population stratification. In Study 1, Lerman and colleagues did not observe any significant $DRD2 \times$ bupropion interactions on smoking outcomes. In a subset of smokers who were enrolled in a randomized, double-blind, placebo-controlled trial of bupropion (291 of 524 enrolled in trial [56%]; Study 2; Brown et al., 2007), David and colleagues evaluated the moderating effects of three candidate gene variants (dopamine transporter *SLC6A3* 3' variable number of tandem repeats, cytochrome P450 2B6 *CPY2B6* C1459T, and *DRD2* Taq1A polymorphisms) and observed a significant $DRD2 \times$ bupropion interaction. Smokers possessing the A2/A2 genotype were more than three times as likely to be abstinent at 6 months of follow-up compared with placebo, but there was virtually no difference in bupropion and placebo efficacy for those with A1/A1 or A1/A2 genotypes (David et al., 2007). However, statistical significance was demonstrated only at the 6-month follow-up.

DNA extraction and polymerase chain reaction techniques and assays for the *DRD2* Taq1A polymorphism have been described previously (Lerman et al., 1999), validated by confirming a polymorphic inheritance in seven human family lines. The *DRD2* Taq1A genotype was classified as the presence or absence of the A1 allele (A1/A1 or A2/A1 vs. A2/A2).

Measures

Demographics and nicotine dependence—Self-reported sex, ancestry, and age were assessed at a baseline interview. Nicotine dependence severity was assessed with the Fagerström Test for Nicotine Dependence (validated, six-item self-reported measure of nicotine dependence; Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

Smoking cessation—Point-prevalence abstinence, defined as 7-day biochemically verified abstinence, validated using salivary cotinine levels (≤ 15 ng/ml) by a gas–liquid chromatography method (Feyerabend & Russell, 1990), was assessed at 10 weeks (end of treatment at 9 weeks post target quit date; EOT) and at 6-month and 12-month follow-ups (Society for Research on Nicotine and Tobacco, 2002).

Data analyses

We used generalized estimating equations (GEEs; Zeger & Liang, 1986) to analyze biochemically verified 7-day point-prevalence abstinence at EOT, 6 months, and 12 months (Society for Research on Nicotine and Tobacco, 2002), including sex and FTND scores as covariates, and the linear effect of time, prior to entering main effects. All tests of interactions included lower-order interactions and were conducted in R (www.r-project.org/) using GEEPACK (Halekoh, Hojsgaard, & Yan, 2006) with the Logit link function and an unstructured correlation matrix specified.

Based on a genotype relative risk (Cardon, Idury, Harris, Witte, & Elston, 2000) of 3, as observed for the *DRD2* Taq1A polymorphism (David et al., in press; Lerman et al., 2003), for 2 *df* tests of genotypes, we calculated that a sample size of approximately 400 for one diallelic marker was necessary to achieve 80% power at an alpha of .05.

Results

Characteristics of participants

The pooled study sample consisted of 722 participants of European ancestry (53% female), comprising 431 participants from Study 1 and 291 participants from Study 2. Baseline characteristics (sex, age, ancestry, treatment allocation, cigarettes/day, FTND score, and loss to follow-up) were similar across studies (Table 1), although participants in Study 2 reported somewhat higher FTND scores (6 vs. 5, $p<.05$) and smoked more cigarettes per day (25 vs. 22, $p<.05$). A total of 369 participants received bupropion and 353 received placebo. The mean age of participants was 45 years ($SD=12$), and mean cigarette consumption was 23 cigarettes/day ($SD=10$).

Genotype frequencies (A1/A1: $n=50$, 6.9%; A1/A2: $n=262$, 36.3%, or A2/A2: $n=410$, 56.8%) did not deviate significant from Hardy-Weinberg equilibrium in either the individual or pooled samples (p values $>.46$). Genotype was not associated with any socio-demographic variable, treatment group assignment, or nicotine dependence severity (p values $>.22$).

Genotype and smoking cessation

Given significant associations with rates of abstinence, we included sex ($B=-0.44$, $SE=0.16$, $p<.008$), cigarettes/day ($B=-0.02$, $SE=0.01$, $p<.05$), and study site ($B=0.26$, $SE=0.10$, $p<.02$) as covariates in all analyses examining the associations between main effects and continuous abstinence at the three follow-up assessments. Participant characteristics (including abstinence rates at EOT by genotypic stratum) are presented in Table 2.

The test of main effects suggested higher rates of abstinence among individuals who received bupropion ($B=0.74$, $SE=0.17$, $p<.001$) compared with placebo. Although we did not find a main effect of *DRD2* genotype on abstinence ($B=-0.12$, $SE=0.17$, $p>.40$), we did find a significant two-way interaction between *DRD2* genotype and bupropion ($B=0.87$, $SE=0.34$, $p=.009$). Moreover, the three-way interaction between *DRD2* genotype, bupropion, and the linear effect of time in the same model, with all lower-order interactions, was not significant ($p>.24$), suggesting that the rate of relapse over time was not different across *DRD2* genotype groups in the bupropion and placebo conditions.

The adjusted odds ratios for cessation were for A2/A2: $OR=3.25$ (95% CI 2.00–5.28) at EOT, $OR=2.81$ (95% CI 1.66–4.77) at 6 months, and $OR=1.70$ (95% CI 0.95–3.05) at 12 months, and for A1/A1 or A1/A2: $OR=1.15$ (95% CI 0.58–2.29) at EOT, $OR=1.19$ (95% CI 0.68–2.08) at 6 months, and $OR=1.09$ (95% CI 0.57–2.11) at 12 months (abstinence rates demonstrated in Figure 1). Abstinence rates for each study site individually and combined stratified by treatment group and *DRD2* genotype are indicated in Table 3.

Discussion

The results of our pooled analysis of the combined data from two clinical trials suggest that *DRD2* Taq1A genotype influences response to bupropion for smoking cessation. The observation that the *DRD2* $\times$ bupropion interaction was significant, independent of the linear effect of time, is novel, and suggests that the lack of statistical significance of this interaction in previous pharmacogenetic analyses was the result of insufficient statistical power to detect the interaction. The sample size supported testing one gene $\times$ treatment interaction, prompting selection of the only polymorphism for which replication data were available, to minimize alpha inflation (Wacholder, Chanock, Garcia-Closas, El Ghormli, & Rothman, 2004). Although viable candidate genes are found throughout the pathway involved in dopamine synthesis, reuptake, receptor function, and degradation, all of which need to be thoroughly evaluated in studies of sufficient sample size to examine multiple genetic loci, we focused our

examination on the *DRD2* Taq1A polymorphism. However, to have sufficient statistical power to conduct a pharmacogenetic analyses of multiple loci, clinical trials of much larger magnitude (5,000 subjects or more) should be performed (Cardon et al., 2000).

We had not anticipated observing associations between *DRD2* Taq1A genotype and FTND score or cigarettes per day, two phenotypes associated with genetic variation in cytochrome alpha 4 nicotine acetylcholine receptor (Feng et al., 2004; Li et al., 2005) and p450 2A6 (Malaiyandi et al., 2006; O'Loughlin et al., 2004; Schoedel, Hoffmann, Rao, Sellers, & Tyndale, 2004) genes, respectively. Given the lack of consistency in the literature with regard to smoking-related trait phenotypes (Munafò, Clark, Johnstone, Murphy, & Walton, 2004), the Taq1A polymorphism has emerged as a more reliable pharmacogenetic endophenotype candidate gene, given apparent moderating effects on bupropion and NRT. A recent meta-analysis (Munafò et al., 2004) that did not find evidence of association between the Taq1A polymorphism and smoking cessation defined *cessation* as a comparison of current smokers and ex-smokers identified in case-control studies, rather than cessation within a cohort of treatment-seeking smokers over time. These phenotypes may reflect differing underlying processes and certainly are not informative with respect to pharmacogenetic gene $\times$ treatment interactions.

The *DRD2* A2/A2 genotype has been associated with increased receptor density (Jonsson et al., 1999). Recent evidence that the Taq1A variant alters an amino acid in the *ANKK1* protein kinase gene, near the *DRD2* locus (Neville et al., 2004), does not rule out an effect on the *DRD2* gene. Data from the HapMap project reveal that the variant is in linkage disequilibrium with other variants in the *DRD2* gene, but not with variants in the *ANKK1* gene. Thus additional functional variants affecting *DRD2* expression may be contributing to the observed association with response to bupropion, as was demonstrated for the *DRD2* -141Cins/del polymorphism, a functional variant associated with increased transcriptional efficiency of the *DRD2* gene, in a separate published report of Study 1 (Lerman et al., 2006).

Another, more speculative possibility is that *ANKK1* may exert an effect on dopaminergic neurotransmission itself. The function of many proteins can be influenced or regulated by a process of phosphorylation of key amino acid residues within the protein, which could influence factors such as the affinity of the protein for ligands that bind to it, such as dopamine to its receptor or its transporter in this instance, and could also influence other aspects of activity. If this were to be so, it might explain how a polymorphism in a gene that was not the receptor itself might relate to dopaminergic activity (D. J. K Balfour, personal communication, June 23, 2006). Data do not currently exist to test this possibility directly.

A similar pattern of pharmacogenetic efficacy has emerged for two polymorphisms associated with D2 receptor activity. Johnstone and colleagues (2004) found that the *DRD2* A1/A1 or A1/A2 genotype was associated with relatively greater efficacy of nicotine replacement therapy patch for smoking cessation compared with A2/A2 genotypes, an effect opposite to what is reported here for bupropion efficacy. Similarly, Lerman and colleagues (2006) reported that a genetic variant (*DRD2* -141Cins) portending greater expression of the *DRD2* gene was associated with greater bupropion efficacy while the low-activity variant (-141Cdel) was associated with greater NRT (patch and nasal spray) efficacy. A tentative pattern is therefore emerging, albeit based on a small number of studies, whereby genotypes associated with reduced D2 receptor availability or function predict better outcomes with NRT, while those associated with normal receptor expression or function predict a better response to bupropion (Lerman et al., 2006).

Mechanistic explanations for these observations require speculation but have focused on differences in the neurological sites of action for both drugs and the notion that, for bupropion

to exert its pharmacodynamic actions, relatively “unaltered” striatal D2 receptor density might be required while NRT might actually be treating withdrawal symptoms in individuals who have relatively reduced striatal dopaminergic tone (David et al., 2007; Lerman et al., 2006). Indeed, we have demonstrated previously that only individuals with A2/A2 genotypes appear to experience reductions in nicotine withdrawal symptoms and that *DRD2* genotype may exert its effects on smoking cessation via craving reduction in individuals using bupropion (David et al., 2007; David et al., 2003).

Additional research, in future trials of markedly larger size, is needed to examine potential moderating effects of sex, whether these effects exist in other populations (e.g., on the basis of ancestry; Munafò, Lerman, Niaura, Shields, & Swan, 2005; Munafò, Shields et al., 2005) and to examine the complex biopsychosocial and ethical implications of genetically tailored therapies for smoking cessation (Marteau & Lerman, 2001). However, if the studies reporting evidence from pharmacogenetic evaluations of NRT and bupropion efficacy are replicated, individuals who may be bupropion nonresponders—in part because of their *DRD2* Taq1A genotypes, may fortuitously derive greater efficacy from the use of NRT.

Acknowledgements

This study was funded in part by U.S. Public Health Service grants HL32318, CA63562, DA08511, CA84719, CA84718, and DA14276-04 and by GlaxoSmithKline, Inc.

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Figure 1.

Smoking cessation outcomes by treatment condition and DRD2 Taq1A genotype. Rate of biochemically verified 7-day point-prevalence abstinence at end of treatment and at 6- and 12-month follow-up assessments grouped by DRD2 Taq1 genotype and treatment condition (A1/A1 or A1/A2 on placebo: solid; A1/A1 or A1/A2 on bupropion: dashed; A2/A2 on placebo (PBO): dotted; A2/A2 on bupropion (BUP): dotted and dashed).

Table 1

Characteristics of study participants.

Variable	Study 1: Georgetown/Buffalo (N=431)	Study 2: Brown University (N=291)	<i>p</i> value for difference ^a
Treatment condition			
Bupropion	233 (54.0%)	136 (46.7%)	.55
Placebo	198 (46.0%)	155 (53.3%)	
Age (years)	44.6 (<i>SD</i> =11.4)	45.5 (<i>SD</i> =10.7)	.34
Sex (female)	234 (54.3%)	148 (50.9%)	.12
Cigarettes/day ^b	21.6 (<i>SD</i> =9.3)	24.6 (<i>SD</i> =9.9)	<.001
Fagerström Test for Nicotine Dependence score ^b	5.1 (<i>SD</i> =2.1)	6.3 (<i>SD</i> =1.9)	<.001
<i>DRD2</i> Taq1A genotype			
A1/A1	28 (6.5%)	22 (7.5%)	.54
A1/A2	155 (36.0%)	107 (36.8%)	
A2/A2	248 (57.5%)	162 (55.7%)	

Note. Values are numbers of subjects with percentages or means with standard deviations.

^aChi-square tests for dichotomous variables, Student *t* tests for continuous variables, and one-way analysis of variance for the categorical variable (*DRD2* Taq1A genotype).

^bData missing for 4 participants (Study 1) and 1 participant (Study 2).

^cData missing for 5 participants (Study 1) and 2 participants (Study 2).

Table 2

Characteristics and outcomes by genotype.

<i>DRD2</i> Taq1 genotype	A1/A1 (<i>n</i> =50)	A1/A2 (<i>n</i> =262)	A2/A2 (<i>n</i> =410)	All participants (<i>n</i> =722)
Age (years)	48.2 (<i>SD</i> =10.6)	44.8 (<i>SD</i> =11.2)	44.7 (<i>SD</i> =11.1)	45.0 (11.2)
Sex (male)	25 (50.0%)	130 (49.6%)	185 (45.1%)	340 (47.1%)
Cigarettes/day ^a	25.1 (<i>SD</i> =11.5)	22.8 (<i>SD</i> =9.2)	22.6 (<i>SD</i> =9.7)	22.9 (<i>SD</i> =9.7)
Fagerström Test for Nicotine Dependence score ^b	6.1 (<i>SD</i> =1.9)	5.4 (<i>SD</i> =2.1)	5.7 (<i>SD</i> =2.1)	5.6 (<i>SD</i> =2.1)
Abstinence (end of treatment)	12 (24.0%)	79 (30.2%)	102 (24.9%)	193 (26.7%)
Abstinence (6 months)	10 (20.0%)	54 (20.6%)	79 (19.3%)	143 (19.8%)
Abstinence (12 months)	7 (14.0%)	35 (13.4%)	55 (13.4%)	97 (13.4%)

Note. Values are means with standard deviations, except for sex and abstinence (number of subjects and percentage).

^aData missing for 5 participants.

^bData missing for 7 participants.

Table 3
Smoking cessation outcomes by treatment condition and DRD2 Taq1A genotype.

Treatment condition	DRD2 Taq1A genotype	Assessment of abstinence	Percent abstinent (number of subjects/sample)		
			Study 1 (N=431)*	Study 2 (N=291)	Pooled data (N=722)*
Bupropion	A1/A1 or A1/A2	End of treatment	25.7 (26/101)	44.4 (28/63)	32.9 (54/164)
Placebo			25.3 (20/79)	25.8 (17/66)	25.5 (37/145)
Bupropion	A2/A2	6 months	29.5 (38/129)	45.2 (33/73)	35.2 (71/202)
Placebo			12.1 (14/116)	19.1 (17/89)	15.1 (31/205)
Bupropion	A1/A1 or A1/A2	6 months	20.8 (21/101)	23.8 (15/63)	22.0 (36/164)
Placebo			12.7 (10/79)	27.3 (18/66)	19.3 (28/145)
Bupropion	A2/A2	12 months	20.9 (27/129)	37.0 (27/73)	26.7 (54/202)
Placebo			10.3 (12/116)	14.6 (13/89)	12.2 (25/205)
Bupropion	A1/A1 or A1/A2	12 months	11.9 (12/101)	17.5 (11/63)	14.0 (23/164)
Placebo			8.9 (7/79)	18.2 (12/66)	13.1 (19/145)
Bupropion	A2/A2	12 months	14.7 (19/129)	19.2 (14/73)	16.3 (33/202)
Placebo			8.6 (10/116)	13.5 (12/89)	10.7 (22/205)

Note. Frequencies for participants at both study sites who reported continuous abstinence with biochemically verified 7-day point prevalence, grouped by treatment condition using intention-to-treat criteria and *DRD2* Taq1A genotype.

^aSmoking outcomes data missing on 6 individuals in Study 1 (3 each for the A1/A1 or A1/A2 group, and for the A2/A2 group).